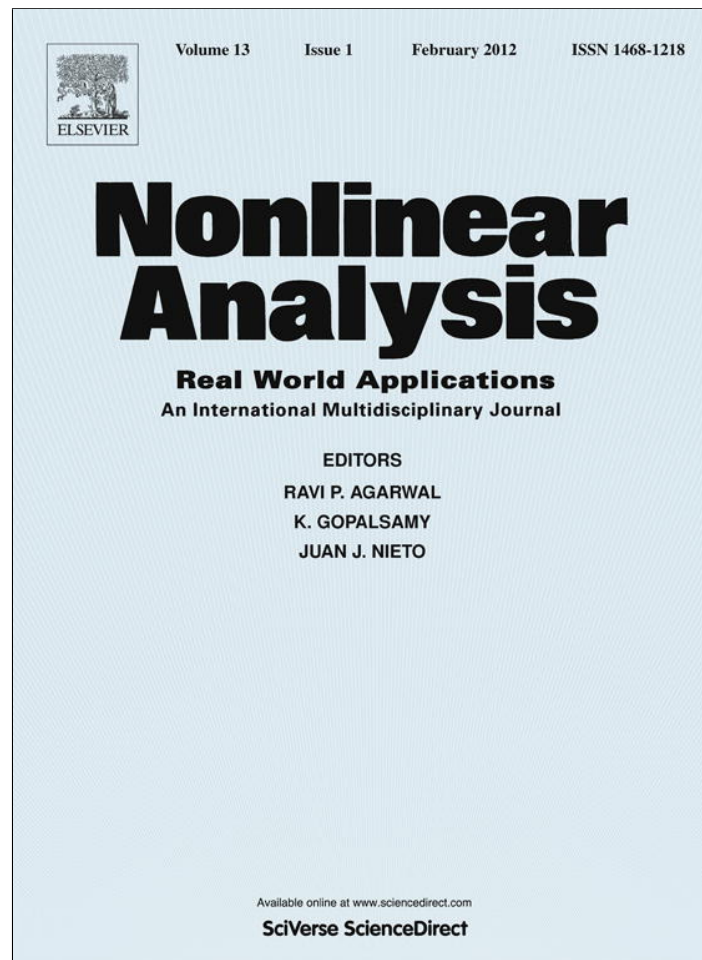


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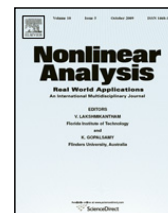
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# Nonlinear Analysis: Real World Applications

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## Periodic solutions of angiogenesis models with time lags

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### ABSTRACT

To enrich the dynamics of mathematical models of angiogenesis, all mechanisms involved are time-dependent. We also assume that the tumor cells enter the mechanisms of angiogenic stimulation and inhibition with some delays. The models under study belong to a special class of nonlinear nonautonomous systems with delays. Explicit sufficient and necessary conditions for the existence of the positive periodic solutions were obtained via topological methods. Numerical examples illustrate our findings. Some open problems are presented for further studies.

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### 1. Introduction

The process which enables a solid tumor to make the transition from the relatively harmless and localized avascular state to the more dangerous vascular state is termed angiogenesis. The angiogenic process is determined by the relative balance of angiogenesis stimulators and inhibitors [1–3]. The two-compartmental model of tumor growth, in response to tumor-derived stimulators and inhibitors, was developed in [4].

$$\begin{aligned}\frac{dx}{dt} &= ax(t) \ln \frac{K(t)}{x(t)} - p(t)x(t) \\ \frac{dK}{dt} &= -cK(t) + S(x(t), K(t)) - I(x(t), K(t)) - q(t)K(t),\end{aligned}$$

where  $x(t)$  is the tumor mass and  $K(t)$  is a variable carrying capacity. According to [4], a stimulator/inhibitor tumor growth dynamics should provide a time dependent carrying capacity under angiogenic control and include the distinct mechanisms for angiogenic stimulation and inhibition. The dynamics of the second equation is a balance between stimulatory and inhibitory effects: the first term is the loss of functional vasculature; the second term corresponds to the stimulatory capacity of the tumor; the third term reflects endogenous inhibition due to endothelial cell death or disaggregation.

An additional insight into clinically observed tumor-induced phenomena, such as tumor recurrence or short and long term tumor oscillations, can be gained by introducing models with the time-varying parameters. It is known (see, for example, [5–7]) that the drugs affect all types of cells, and over time the therapy has more effect on the normal tissue and less effect on the tumor volume; or the drugs might reduce the carrying capacity of the normal cells. The tumor microenvironment plays a crucial role in these processes [8] because the variability of the tumor microenvironment induces

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fluctuations in all mechanisms. The biological interpretations of environmental fluctuations are many, e.g., the degree of vascularization of tissues, the supply of oxygen, the supply of nutrients, the immunological state of the host, chemical agents, temperature and radiations. To determine appropriate treatment schedules the influence of variations in tumor kinetics should be considered. Thus we assume that all mechanisms involved are time-dependent.

To model processes in nature it is frequently required to know system states “after a while”, i.e., models incorporating memory [9]. In cell dynamics the after-effects represent: the time it takes to respond to angiogenic growth factors, divide, migrate to the site of growth; time between activation of vascular precursor cells and construction of functional vessels; time associated with drug-induced cell-kill, or progression delays due to repair of cell damage [10–14]. We assume that the tumor cells enter the mechanisms of angiogenic stimulation and inhibition with some delays  $h(t) \leq t$ .

Following the models developed by Hahnfeldt et al. [4,15], we complement their results by studying model

$$\begin{aligned} \frac{dx}{dt} &= a(t)x(t) \ln \frac{K(t)}{x(t)} - p(t)x(t) \\ \frac{dK}{dt} &= -c(t)K(t) + S(t, x(h(t)), K(t)) - I(t, x(h(t)), K(t)) - q(t)K(t), \end{aligned} \tag{1}$$

where all mechanisms involved are time-dependent. The last terms  $p(t)$  and  $q(t)$  in Model (1) are the varying effectiveness of the drug. If, for example, we assume that the drug combination is administered with a periodicity, then  $p(t)$  and  $q(t)$  can be expressed as exponential decaying functions in  $t$  during each period.

**Remark 1.1.** According to [4],  $S = bK^m x^n$  is a form for the stimulatory mechanism, where  $m + n \approx 1$ . For example,  $S = bx$ , or another choice  $S = bK$  if we follow the hypothesis that the stimulatory factors are independent of the tumor size [1,2].

In particular, we will examine the following models:

Model 1.

$$\begin{aligned} \frac{dx}{dt} &= a(t)x(t) \ln \frac{K(t)}{x(t)} - p(t)x(t) \\ \frac{dK}{dt} &= -c(t)K(t) + b(t)x(h(t)) - d(t)x^{2/3}(h(t))K(t) - q(t)K(t). \end{aligned} \tag{2}$$

Model 2.

$$\begin{aligned} \frac{dx}{dt} &= a(t)x(t) \ln \frac{K(t)}{x(t)} - p(t)x(t) \\ \frac{dK}{dt} &= -c(t)K(t) + b(t)K(t) - d(t)x^{2/3}(h(t))K(t) - q(t)K(t). \end{aligned} \tag{3}$$

We shall assume that  $a, b, c, d, p$  and  $q$  are positive, continuous and  $T$ -periodic and that  $h(t) = t - \tau(t)$  for some continuous and  $T$ -periodic positive function  $\tau$ . By ‘positive periodic solutions’ we mean solutions  $(x, K)$  that are globally defined and satisfy

$$x(t + T) = x(t) > 0, \quad K(t + T) = K(t) > 0$$

for all  $t$ .

Classical models that have been the mainstay for models of cells growth are based on the assumption that the mechanism of the growth rate of tumor cells is a Gompertzian curve

$$\frac{dx}{dt} = rx(t)G(x(t)),$$

where  $G(x) = \alpha - \beta \ln x(t)$ . Here  $\alpha$  is the intrinsic growth rate of the tumor, i.e., a parameter related to the initial mitosis rate;  $\beta$  is the growth inhibition factor, related to the antiangiogenic process. For the Gompertz model the inhibition logarithmic function  $G(x)$  and its derivative are more likely to cause chaotic (abruptive) behavior. According to the recent experimental data [16] (see also [17]), the Gompertz model is not suitable for extrapolating the specific growth rate (or generation time) of the cells when the concentration is low and/or at the early stage of cell development. Therefore, a logistic-type model with Richards nonlinearity could also be used for modeling tumor growth dynamics (see, for example, [4]).

Model 3.

$$\begin{aligned} \frac{dx}{dt} &= a(t)x(t) \left( 1 - \left[ \frac{x(t)}{K(t)} \right]^m \right) - p(t)x(t) \\ \frac{dK}{dt} &= -c(t)K(t) + b(t)x(h(t)) - d(t)x^{2/3}(h(t))K(t) - q(t)K(t). \end{aligned} \tag{4}$$

Here  $m > 0$  and  $m \neq 1$  is a constant that drops an unnatural symmetry of the classical logistic curve ( $m = 1$ ).

Note that all autonomous models without time lags were studied in [18,4,15]. In [19], autonomous models with time-varying delays were introduced, explicit conditions for the existence of positive global solutions and the equilibria solutions were obtained. Based on the results obtained in [20–24], we found explicit sufficient conditions for the existence of the local attractors for Model 1 and Model 2.

The fact that malignant tumors have periods in which they grow rapidly, often though not invariably followed by a latent stage, has been known by clinicians for many years. The existence of periodic positive solutions (cancer periodicity) of models i.e., after cessation of treatment the original periodic rhythm returns, is a very important issue in cancer research (2)–(4). For the constant dose of the drug it is possible to find a dose such that the equilibrium point is equal to zero, whereas in a periodic microenvironment, suppression or eradication of the tumor depends on the shape of pulses in the periodic protocol. According to [5], chemotherapy treatment with a period commensurate with the normal cell cycle time could also minimize the normal cell kill. Therefore, the prediction of the oscillations in the concentrations of cells in the various phases of the cell cycle may drastically increase the efficacy of resonance chemotherapy [5,25].

A model for tumor growth in [26] that combines multiple effects, such as periodicity of the environment, time delays and impulse actions is a step toward new ways to understand the complex tumor dynamics. Based on the contraction mapping principle, sufficient conditions for the existence and exponential stability of the positive non-periodic (almost periodic) solutions were obtained in [26].

Partial differential equations (PDEs) have been also used extensively to model spatial aspects of solid tumor growth and cancer-immune system interactions, and have been discussed in many research papers (e.g., [27–34]). For example, a class of nonlinear PDEs, with quadratic type nonlinearity, that models complex multicellular systems was introduced in [27]. The asymptotic analysis refers to the derivation of hyperbolic models focused on the influence of existence of a global equilibrium solution. A model arising in angiogenesis, that includes a chemotaxis type term and a nonlinear boundary condition at the tumor boundary, was under study in [28]. It was shown that the parabolic problem admits a unique positive global solution. One second-order PDE that approximates a tumor invasion model was under study in [30]. In [32] a model of cancer invasion with tissue remodeling was under study. Under a restrictive assumption on the coefficients, the global existence, boundedness and uniqueness of classical solutions were obtained by establishing some a priori estimates. In [33], a PDE model of tumor angiogenesis that describes the angiogenic response of endothelial cells to a secondary tumor, is under study. By using topological methods, it was proved that the PDE system has a unique global solution. In [34], a mathematical model describing the growth of a solid in the presence of an immune system response was under investigation via the reaction–diffusion PDE system. By using the approximation method combined with energy estimates and the bootstrap arguments, it was proved that this system has a global classical solution.

In this paper we are focused on models (2)–(4), and based on the topological degree theory, proved the existence of periodic solutions of all models, illustrated by the numerical examples. Necessary and sufficient conditions for the existence theorems are explicit, and for each model we obtained upper and lower estimates for the solutions. Finally, we formulate some open problems.

## 2. Preliminaries

Substitution  $u = \ln x, v = \ln K$  yields:

for model (2)

$$\begin{aligned} \frac{du}{dt} &= a(t)(v(t) - u(t)) - p(t) \\ \frac{dv}{dt} &= b(t)e^{u(h(t))-v(t)} - c(t) - d(t)e^{2/3u(h(t))} - q(t), \end{aligned} \tag{5}$$

for model (3)

$$\begin{aligned} \frac{du}{dt} &= a(t)(v(t) - u(t)) - p(t) \\ \frac{dv}{dt} &= b(t) - c(t) - d(t)e^{2/3u(h(t))} - q(t), \end{aligned} \tag{6}$$

and for model (4)

$$\begin{aligned} \frac{du}{dt} &= a(t)(1 - e^{m(u(t)-v(t))}) - p(t) \\ \frac{dv}{dt} &= b(t)e^{u(h(t))-v(t)} - c(t) - d(t)e^{2/3u(h(t))} - q(t). \end{aligned} \tag{7}$$

Several methods are used for the first order periodic systems; among them, one of the best known is based on the Poincaré operator, defined in terms of the solutions of the associated initial value problem. This requires some information about the flow of the differential equation; for instance, it is needed to know in advance if, for some choice of the initial data, solutions starting at  $t = 0$  are defined over  $[0, T]$ . In contrast with this situation, topological degree methods allow to avoid any consideration about the flow by studying an equivalent functional equation.

For the reader's convenience, we present the basic facts of the degree theory that are used in this paper.

Roughly speaking, the topological degree is an algebraic count of the zeros of a continuous function  $f : \bar{U} \rightarrow E$  where  $U$  is an open and bounded subset of a Banach Space  $E$ , and  $f$  does not vanish on  $\partial U$ . Let  $E = \mathbb{R}^n$ . A function  $f \in C^1$  has 0 as a regular value, if the differential  $Df(x) : \mathbb{R}^n \rightarrow \mathbb{R}^n$  is surjective for every  $x \in f^{-1}(0)$ . We define Brouwer degree of  $f$  as

$$\text{deg}_B(f, U, 0) := \sum_{x \in f^{-1}(0) \cap U} \text{sgn} Jf(x), \tag{8}$$

where  $Jf$  denotes the Jacobian of  $f$ , namely  $Jf(x) = \det Df(x)$ . This definition can be extended in an appropriate way for  $f \in C$  with  $f \neq 0$  on  $\partial U$ .

Further generalization for infinite dimensional spaces is given by the Leray–Schauder degree, which is defined for Fredholm operators  $f : \bar{U} \rightarrow E$  of the type  $f = I - \mathcal{K}$  with  $\mathcal{K}$  compact. In particular, when the range of  $\mathcal{K}$  is contained in a finite dimensional subspace  $V \subset E$ , the Leray–Schauder degree is defined by

$$\text{deg}_{LS}(f, U, 0) := \text{deg}_B(f|_V, U \cap V, 0). \tag{9}$$

More remarkable properties of the degree can be found for example in [35], however, in the present work, we will only use two of them:

1. If  $\text{deg}(f, U, 0) \neq 0$ , then  $f$  vanishes in  $U$ .
2. Homotopy invariance: if  $F : \bar{U} \times [0, 1] \rightarrow E$  is continuous such that  $I - F(\cdot, \lambda)$  is compact for all  $\lambda$  and  $F(u, \lambda) \neq 0$  for  $u \in \partial U$  and  $\lambda \in [0, 1]$ , then  $\text{deg}_{LS}(F(\cdot, \lambda), U, 0)$  does not depend on  $\lambda$ .

Consider the spaces

$$C_T : \{u \in C(\mathbb{R}) : u(t) = u(t + T)\}, \quad \tilde{C}_T : \{u \in C_T : \bar{u} = 0\},$$

where  $\bar{u}$  denotes the average of the function  $u(t)$  on  $[0, T]$ , namely  $\bar{u} := \frac{1}{T} \int_0^T u(t) dt$ .

According to the standard continuation method [36], we shall convert each of the problems under study into an equivalent equation  $F(u, v) = (0, 0)$  for some continuous  $F : C_T \times C_T \rightarrow C_T \times C_T$ ; and embed it in a continuous one-parameter family of problems  $F_\lambda(u, v) = (0, 0)$ , where  $F_1 = F$ , and each  $F_\lambda$  has the form  $F_\lambda = I - \mathcal{K}_\lambda$ , with  $\mathcal{K}_\lambda : C_T \times C_T \rightarrow C_T \times C_T$  compact. Thus, using the homotopy invariance of the degree, it will suffice to find a bounded domain  $\Omega \subset C_T \times C_T$  such that

1.  $F_\lambda$  does not vanish on  $\partial\Omega$  for  $0 \leq \lambda < 1$ .
2.  $\text{deg}_{LS}(F_0, \Omega, 0) \neq 0$ .

**Remark 2.1.** In all cases, we define the operators in such a way that the range of  $\mathcal{K}_0$  is contained in  $\mathbb{R}^2$ , regarded as a 2-dimensional subspace of  $C_T \times C_T$ ; thus, according to (9), the Leray–Schauder degree  $\text{deg}_{LS}(F_0, \Omega, 0)$  will be computed as the Brouwer degree  $\text{deg}_B(f, U, 0)$ , where  $f := F_0|_{\mathbb{R}^2} : \mathbb{R}^2 \rightarrow \mathbb{R}^2$  and  $U := \Omega \cap \mathbb{R}^2$ . Furthermore, since  $f$  is a  $C^1$  function and 0 is a regular value, the previous formula (8) applies.

In order to establish an appropriate setting for solving all systems (5)–(7), we shall define the corresponding integral operators. Firstly, observe that for any  $\varphi \in C_T$  and  $\psi \in \tilde{C}_T$  the problems

$$u'(t) + a(t)u(t) = \varphi(t), \quad v'(t) = \psi(t)$$

have unique solutions  $u \in C_T$  and  $v \in \tilde{C}_T$ . This allows us to define operators  $K_a : C_T \rightarrow C_T$  and  $K_0 : \tilde{C}_T \rightarrow \tilde{C}_T$  given by

$$K_a(\varphi) = u, \quad K_0(\psi) = v.$$

A simple computation shows that

$$K_a(\varphi) = \left( \frac{\int_0^T \varphi(s) e^{\int_0^s a(r) dr} ds}{e^{\int_0^T a(r) dr} - 1} + \int_0^t \varphi(s) e^{\int_0^s a(r) dr} ds \right) e^{-\int_0^t a(r) dr},$$

and

$$K_0(\psi) = \int_0^t \psi(s) ds - \frac{1}{T} \int_0^T \int_0^s \psi(r) dr ds.$$

Note that the integral operators, defined by first order systems, are similar to those used in the Samoilenko numerical–analytical method (see e.g. [37]). An application of Arzelá–Ascoli's Theorem shows that  $K_a$  and  $K_0$  are compact operators.

**Remark 2.2.** In all cases, we define the operators in such a way that the range of  $\mathcal{K}_0$  is contained in  $\mathbb{R}^2$ , regarded as a 2-dimensional subspace of  $C_T \times C_T$ ; thus, the Leray–Schauder degree  $\text{deg}_{LS}(F_0, \Omega, 0)$  can be easily computed as the Brouwer degree  $\text{deg}_B(f, U, 0)$ , where  $f := F_0|_{\mathbb{R}^2} : \mathbb{R}^2 \rightarrow \mathbb{R}^2$  and  $U := \Omega \cap \mathbb{R}^2$ . Furthermore, since  $f$  is a  $C^1$  function and 0 is a regular

value, its degree is simply defined as

$$\sum_{x \in f^{-1}(0) \cap U} \text{sgn} Jf(x),$$

where  $Jf$  denotes the Jacobian determinant of  $f$ , namely  $Jf(x) = \det Df(x)$ .

For Model 1 and Model 2, we set

$$F_\lambda(u, v) = (u, v) - (K_a(\Phi_\lambda), \bar{v} + \bar{\Psi}_1 + K_0(\Psi_\lambda - \bar{\Psi}_\lambda)),$$

where for Model 1 the continuous operators  $\Phi_\lambda$  and  $\Psi_\lambda : C_T \times C_T \rightarrow C_T$  are defined by

$$\Phi_\lambda = \Phi_\lambda(v) := \lambda(a(t)v(t) - p(t))$$

and

$$\Psi_\lambda = \Psi_\lambda(u, v) := \lambda(b(t)e^{u(h(t))-v(t)} - c(t) - q(t) - d(t)e^{\frac{2}{3}u(h(t))}). \tag{10}$$

Whereas for Model 2, the operators  $\Phi_\lambda$  and  $\Psi_\lambda$  are defined as

$$\Phi_\lambda = \Phi_\lambda(v) := a(t)(1 - \lambda)\bar{v} + \lambda(a(t)v(t) - p(t)),$$

and

$$\Psi_\lambda = \Psi_\lambda(u) := \lambda(b(t) - c(t) - q(t) - d(t)e^{\frac{2}{3}u(h(t))}).$$

When  $0 < \lambda \leq 1$ ,  $F_\lambda(u, v) = (0, 0)$  if and only if  $(u, v) \in C_T \times C_T$  is a solution of the system

$$\begin{cases} u'(t) + a(t)u(t) = \Phi_\lambda \\ v'(t) = \Psi_\lambda. \end{cases} \tag{11}$$

Indeed, if  $F_\lambda(u, v) = 0$  then  $u = K_a(\Phi_\lambda)$  and hence  $u' + au = \Phi_\lambda$ . Moreover, taking average at both sides of the equality

$$v = \bar{v} + \bar{\Psi}_1 + K_0(\Psi_\lambda - \bar{\Psi}_\lambda)$$

we deduce that  $\bar{\Psi}_1 = 0$  and then  $\bar{\Psi}_\lambda = 0$ . This implies that  $v = \bar{v} + K_0(\Psi_\lambda)$  and consequently  $v' = \Psi_\lambda$ . Conversely, the equality  $u' + au = \Phi_\lambda$  obviously implies that  $u = K_a(\Phi_\lambda)$  and, on the other hand, from the equality  $v' = \Psi_\lambda$  and the periodicity of  $v$  we deduce that  $\bar{\Psi}_\lambda = 0$  and then  $\bar{\Psi}_1 = 0$ . Moreover, as  $(v - \bar{v})' = \Psi_\lambda$  it follows that  $v - \bar{v} = K_0(\Psi_\lambda)$  which, in turn, implies that  $v = \bar{v} + \bar{\Psi}_1 + K_0(\Psi_\lambda - \bar{\Psi}_\lambda)$ .

To examine Model 3, we assume

$$F_\lambda(u, v) := (u, v) - (\bar{u} + \bar{\Phi}_1 + K_0(\Phi_\lambda - \bar{\Phi}_\lambda), \bar{v} + \bar{\Psi}_1 + K_0(\Psi_\lambda - \bar{\Psi}_\lambda)),$$

where

$$\Phi_\lambda = \Phi_\lambda(u, v) := \lambda(a(t)(1 - e^{m(u-v)}) - p(t))$$

and  $\Psi_\lambda$  is defined by (10).

Proceeding as we did before with the second equation of (11), for  $0 < \lambda \leq 1$  it is seen that  $F_\lambda(u, v) = (0, 0)$  if and only if  $(u, v) \in C_T \times C_T$  is a solution of the system

$$\begin{cases} u'(t) = \Phi_\lambda \\ v'(t) = \Psi_\lambda. \end{cases} \tag{12}$$

In all cases, it follows from the definition of  $\Phi_\lambda$  and  $\Psi_\lambda$  that  $(u, v) \in C_T \times C_T$  is a solution if and only if  $F_1(u, v) = (0, 0)$ . Thus, it will suffice to prove that  $F_1$  has at least one zero in the set

$$\Omega := \{(u, v) \in C_T \times C_T : \alpha < u(t), v(t) < \beta \ \forall t \in \mathbb{R}\}$$

for some constants  $\alpha < \beta$  to be determined for each model. In the next section, we obtain appropriate upper and lower bounds for the solutions of systems (11) and (12). Since the computations vary slightly for each case, our results are presented separately.

### 3. Main results

In this section, we establish sufficient conditions for solving Models 1–3. For convenience, the maximum and the minimum values of a function  $\varphi \in C_T$  will be denoted respectively by  $\varphi_{max}$  and  $\varphi_{min}$ .

#### 3.1. Existence of periodic solutions for model 1

**Theorem 3.1.** Assume that  $b(t) > (c(t) + q(t))e^{(p/a)_{max}}$  for all  $t$ . Then problem (2) admits at least one positive  $T$ -periodic solution.

**Proof.** For  $(u, v) \in \mathbb{R}^2$ , it is easy to check that

$$F_0(u, v) = (u, \bar{c} + \bar{q} + \bar{d}e^{2/3u} - \bar{b}e^{u-v}).$$

Then  $F_0(u, v) = (0, 0)$  if and only if  $u = 0$  and  $v = \ln \frac{\bar{b}}{\bar{c} + \bar{q} + \bar{d}}$ . Thus, if we fix the constants  $\alpha < 0 < \beta$  satisfying the inequality

$$\alpha < \ln \frac{\bar{b}}{\bar{c} + \bar{q} + \bar{d}} < \beta,$$

then  $F_0$  vanishes at exactly one point  $P \in (\alpha, \beta) \times (\alpha, \beta)$ , with

$$DF_0(P) = \begin{pmatrix} 1 & 0 \\ -\left(\bar{c} + \bar{q} + \frac{\bar{d}}{3}\right) & \bar{c} + \bar{q} + \bar{d} \end{pmatrix}.$$

Hence,

$$\text{deg}_{LS}(F_0, \Omega, 0) = \text{deg}_B(F_0|_{\mathbb{R}^2}, (\alpha, \beta) \times (\alpha, \beta), 0) = 1.$$

Suppose that  $F_\lambda(u, v) = (0, 0)$  for some  $\lambda \in (0, 1)$ . If  $\eta$  is a maximum or a minimum of the function  $u$ , then from the first equation of system (11)

$$u(\eta) = \lambda \left( v(\eta) - \frac{p(\eta)}{a(\eta)} \right),$$

and we conclude that

$$u_{\max} \leq \lambda \left( v_{\max} - \left( \frac{p}{a} \right)_{\min} \right),$$

$$u_{\min} \geq \lambda \left( v_{\min} - \left( \frac{p}{a} \right)_{\max} \right).$$

Moreover, if  $\xi$  is a critical point of  $v$ , then

$$b(\xi)e^{u(h(\xi)) - v(\xi)} = c(\xi) + q(\xi) + d(\xi)e^{2/3u(h(\xi))}. \tag{13}$$

Assume firstly that  $\xi$  is a global maximum. If  $v_{\max} \leq \left(\frac{p}{a}\right)_{\min}$ , then  $u_{\max} \leq 0$ ; otherwise,  $u(h(\xi)) - v_{\max} < -\left(\frac{p}{a}\right)_{\min}$ , and we deduce

$$e^{2/3u(h(\xi))} < \left( \frac{be^{-(p/a)_{\min}} - c - q}{d} \right)_{\max}.$$

Thus,

$$u(h(\xi)) < \frac{3}{2} \ln \left( \frac{be^{-(p/a)_{\min}} - c - q}{d} \right)_{\max} := k_1$$

and, using (13) and the fact that  $v(\xi) = v_{\max}$  we obtain:

$$c(\xi) + q(\xi) < b(\xi)e^{k_1}e^{-v_{\max}}.$$

The latter implies

$$u_{\max} + \left(\frac{p}{a}\right)_{\min} < v_{\max} < k_1 + \ln \left( \frac{b}{c + q} \right)_{\max}.$$

Hence, we may fix  $\beta$  such that

$$\beta > \max \left\{ k_1 + \ln \left( \frac{b}{c + q} \right)_{\max}, \left(\frac{p}{a}\right)_{\min} \right\}.$$

Next, if  $\xi$  is a global minimum of  $v$  then (13) holds and

$$u(h(\xi)) - v_{\min} < \ln \frac{c(\xi) + q(\xi) + d(\xi)e^{2/3[\beta - (p/a)_{\min}]}}{b(\xi)} := M(\xi).$$

Hence (13) yields

$$u(h(\xi)) < v_{\min} + \ln \frac{c(\xi) + q(\xi) + d(\xi)e^{2/3[v_{\min} + M(\xi)]}}{b(\xi)}.$$

Using the fact that  $\ln(x + h) < \ln(x) + \frac{h}{x}$  for  $h, x > 0$ , we obtain

$$u(h(\xi)) < v_{\min} + \ln\left(\frac{c+q}{b}\right)_{\max} + \gamma e^{2/3v_{\min}},$$

where

$$\gamma := \left(\frac{de^{2/3M}}{c+q}\right)_{\max}. \tag{14}$$

In consequence,

$$u_{\min} < v_{\min} + \ln\left(\frac{c+q}{b}\right)_{\max} + \gamma e^{2/3v_{\min}}.$$

If  $v_{\min} \geq (\frac{p}{a})_{\max}$ , then  $u_{\min} \geq 0$ , or otherwise,  $v_{\min} < u_{\min} + (\frac{p}{a})_{\max}$  and we conclude:

$$\left(\frac{p}{a}\right)_{\max} + \ln\left(\frac{c+q}{b}\right)_{\max} + \gamma e^{2/3v_{\min}} > 0,$$

namely

$$v_{\min} > \frac{3}{2} \ln \frac{\ln\left(\frac{b}{c+q}\right)_{\min} - (\frac{p}{a})_{\max}}{\gamma}.$$

Thus, it suffices to choose

$$\alpha < \min \left\{ \frac{3}{2} \ln \frac{\ln\left(\frac{b}{c+q}\right)_{\min} - (\frac{p}{a})_{\max}}{\gamma} - \left(\frac{p}{a}\right)_{\max}, \ln \frac{\bar{b}}{\bar{c} + \bar{q} + \bar{d}}, 0 \right\}. \quad \square$$

**Corollary 3.1.** *The following upper estimates hold for the solutions of Model 1*

$$u_{\max} + \left(\frac{p}{a}\right)_{\min} \leq v_{\max} < k_1 + \ln\left(\frac{b}{c+q}\right)_{\max}.$$

Moreover, if the assumption of [Theorem 3.1](#) is satisfied, then the following lower estimates also hold

$$u_{\min} + \left(\frac{p}{a}\right)_{\max} \geq v_{\min} > \frac{3}{2} \ln \frac{\ln\left(\frac{b}{c+q}\right)_{\min} - (\frac{p}{a})_{\max}}{\gamma}$$

with  $\gamma$  as in (14) and  $\beta = k_1 + \ln\left(\frac{b}{c+q}\right)_{\max}$ .

### 3.2. Existence of periodic solutions for model 2

**Theorem 3.2.** *Assume that  $b(t) > c(t) + q(t)$  for all  $t$ . Then problem (3) admits at least one positive  $T$ -periodic solution.*

**Proof.** For  $(u, v) \in \mathbb{R}^2$ , we have

$$F_0(u, v) = (u - v, \bar{c} + \bar{q} + \bar{d}e^{2/3u} - \bar{b}).$$

Thus, if  $\alpha$  and  $\beta$  satisfy

$$e^{2/3\alpha} < \frac{\bar{b} - \bar{c} - \bar{q}}{\bar{d}} < e^{2/3\beta},$$

then  $F_0$  vanishes at exactly one point  $P \in (\alpha, \beta)^2$ , with

$$DF_0(P) = \begin{pmatrix} 1 & -1 \\ \frac{2}{3}(\bar{b} - \bar{c} - \bar{q}) & 0 \end{pmatrix}$$

Hence,

$$\deg_{LS}(F_0, \Omega, 0) = \deg_B(F_0|_{\mathbb{R}^2}, (\alpha, \beta) \times (\alpha, \beta), 0) = 1.$$



As in the previous case, we shall find *a priori* bounds for the solutions of  $F_\lambda(u, v) = (0, 0)$  for  $\lambda \in (0, 1)$ . From system (11), if  $\xi$  is a critical point of  $v$ , then

$$u(h(\xi)) = \frac{3}{2} \ln \frac{b(\xi) - c(\xi) - q(\xi)}{d(\xi)}$$

and hence

$$u_{max} \geq \frac{3}{2} \ln \left( \frac{b - c - q}{d} \right)_{min}, \quad u_{min} \leq \frac{3}{2} \ln \left( \frac{b - c - q}{d} \right)_{max}.$$

On the other hand, if  $\eta$  is a maximum or a minimum of  $u$ , then

$$u(\eta) = (1 - \lambda)\bar{v} + \lambda v(\eta) - \lambda \frac{p(\eta)}{a(\eta)},$$

and we conclude that

$$\begin{aligned} u_{max} &\leq v_{max} - \lambda \left( \frac{p}{a} \right)_{min}, \\ u_{min} &\geq v_{min} - \lambda \left( \frac{p}{a} \right)_{max}. \end{aligned}$$

Moreover, by the periodicity of  $v$  there exist values  $t_{min} < t_{max}$  such that  $t_{max} - t_{min} \leq T$  and  $v_{max} = v(t_{max})$ ,  $v_{min} = v(t_{min})$ . Thus, for some mean value  $\theta$

$$v_{max} - v_{min} = v'(\theta)(t_{max} - t_{min}) \leq T\Psi_\lambda(u)(\theta) < T(b - c - q)_{max} := R. \tag{15}$$

Combined with the previous inequalities, inequality (15) implies that

$$u_{max} - u_{min} < R + \lambda \left[ \left( \frac{p}{a} \right)_{max} - \left( \frac{p}{a} \right)_{min} \right] < R + \left( \frac{p}{a} \right)_{max} - \left( \frac{p}{a} \right)_{min},$$

and consequently

$$\begin{aligned} u_{max} &< R + \left( \frac{p}{a} \right)_{max} - \left( \frac{p}{a} \right)_{min} + \frac{3}{2} \ln \left( \frac{b - c - q}{d} \right)_{max} := M^+, \\ u_{min} &> \frac{3}{2} \ln \left( \frac{b - c - q}{d} \right)_{min} - R + \left( \frac{p}{a} \right)_{min} - \left( \frac{p}{a} \right)_{max} := M^-. \end{aligned}$$

Integration of the first equation of system (11) yields

$$\bar{v} = \bar{u} + \lambda \overline{p/a}$$

which, in turn, implies:

$$\begin{aligned} v_{max} &\leq \bar{v} + R < M^+ + \overline{p/a} + R, \\ v_{min} &\geq \bar{v} - R > M^- - R. \end{aligned}$$

To complete the proof, it suffices to choose

$$\alpha = M^- - R \quad \text{and} \quad \beta = M^+ + \overline{p/a} + R. \quad \square$$

**Corollary 3.2.** *The following upper estimates hold for Model 2*

$$u_{max} < M^+ \quad \text{and} \quad v_{max} < M^+ + \overline{p/a} + R.$$

Moreover, if the assumption of Theorem 3.2 is satisfied, then the following lower estimates also hold

$$u_{min} > M^- \quad \text{and} \quad v_{min} > M^- - R.$$

**3.2.1. Alternative approach**

For simplicity, denote  $u = u(t)$ ,  $u \circ h = u(h(t))$ ,  $a = a(t)$ ,  $b = b(t)$ ,  $c = c(t)$ ,  $d = d(t)$ ,  $p = p(t)$  and  $q = q(t)$ . If  $a(t)$  and  $p(t)$  are smooth functions, an alternative existence result for Model 2 is obtained from the equivalent second order Liénard type equation

$$u'' + \left( a - \frac{a'}{a} \right) u' = a \left( b - c - q - \left( \frac{p}{a} \right)' \right) - ade^{2/3u \circ h} := \Phi(u).$$

In fact, it can be proven that the inequality

$$b > c + q + \left(\frac{p}{a}\right)' \tag{16}$$

for all  $t$  is a sufficient condition for the existence of  $T$ -periodic solutions. We give a sketch of the proof here; the details are left to the reader.

A simple computation shows that, for  $\varphi \in C_T$ , the problem

$$u'' + \left(a - \frac{a'}{a}\right) u' = \varphi$$

has a solution  $u \in \tilde{C}_T$  (which is unique) if and only if  $\int_0^T \theta \varphi dt = 0$ , where  $\theta = \frac{1}{a}$ . Hence, we may define a compact operator

$$K : \left\{ \varphi \in C_T : \int_0^T \theta \varphi dt = 0 \right\} \rightarrow \tilde{C}_T$$

given by  $K(\varphi) = u$ , and  $F_\lambda : C_T \rightarrow C_T$  defined by

$$F_\lambda(u) := u - \bar{u} - P(u) - \lambda K \left( \Phi(u) - \frac{\theta P(u)}{\int_0^T \theta^2(t) dt} \right)$$

where  $P(u) = \int_0^T \theta(t) \Phi(u)(t) dt$ .

Next, for  $\lambda > 0$ ,  $F_\lambda(u) = 0$  if and only if

$$u'' + \left(a - \frac{a'}{a}\right) u' = \lambda \Phi(u).$$

Moreover,  $F_0|_{\mathbb{R}} = -P|_{\mathbb{R}}$ ; namely, for  $u \in \mathbb{R}$

$$F_0(u) = e^{2/3u} \int_0^T d dt + \int_0^T c + q - b dt.$$

Clearly, if inequality (16) holds, then  $F_0(-u) < 0 < F_0(u)$  for  $u \gg 0$  and therefore  $\deg(F_0|_{\mathbb{R}}, (-R, R), 0) = 1$  for large enough  $R$ . On the other hand, if  $F_\lambda(u) = 0$  for  $\lambda \in (0, 1)$ , then  $P(u) = 0$  and

$$\left| u'' + \left(a - \frac{a'}{a}\right) u' \right| \leq a \left( b - c - q - \left(\frac{p}{a}\right)' \right) + ade^{2/3uoh},$$

which implies

$$\int_0^T \theta \left| u'' + \left(a - \frac{a'}{a}\right) u' \right| dt \leq 2 \int_0^T b - c - q dt.$$

Hence

$$\int_0^T \left| u'' + \left(a - \frac{a'}{a}\right) u' \right| dt \leq \frac{2}{\theta_{min}} \int_0^T b - c - q dt := r.$$

From the periodicity of  $u(t)$  there exists  $t_0$  such that  $u'(t_0) = 0$ , then setting  $A(t) := \int_0^t \left(a - \frac{a'}{a}\right) dt$  we obtain:

$$e^{A(t)} u'(t) = \int_{t_0}^t [e^{A(s)} u'(s)]' ds = \int_{t_0}^t e^{A(s)} \left[ u'' + \left(a - \frac{a'}{a}\right) u' \right] ds;$$

thus

$$\|u'\|_\infty \leq re^{A_{max}-A_{min}}, \quad \|u - \bar{u}\|_\infty \leq Tre^{A_{max}-A_{min}}.$$

Finally, the equality  $P(u) = 0$  can be written in the following form

$$e^{2/3\bar{u}} \int_0^T de^{2/3[u(h(t))-\bar{u}]} dt = \int_0^T b - c - q dt.$$

The latter implies that  $|\bar{u}|$  cannot be arbitrarily large; or, in other words, we proved the existence of such  $R$  that  $u \notin \partial B_R(0)$ , and  $\deg(F_1, B_R(0), 0) = 1$ .

3.3. Existence of periodic solutions for model 3

**Theorem 3.3.** Assume that  $(\frac{c(t)+q(t)}{b(t)})^m + (\frac{p}{a})_{max} < 1$  for all  $t$ . Then problem (4) admits at least one positive  $T$ -periodic solution.

**Proof.** In this case, for  $(u, v) \in \mathbb{R}^2$

$$F_0(u, v) = (\bar{p} - \bar{a}[1 - e^{m(u-v)}], \bar{c} + \bar{q} + \bar{d}e^{2/3u} - \bar{b}e^{u-v}).$$

The unique zero of this function corresponds to the point  $P = (u, v)$  given by

$$u = \frac{3}{2} \ln \frac{\bar{b} \left(1 - \frac{\bar{p}}{\bar{a}}\right)^{1/m} - \bar{c} - \bar{q}}{\bar{d}},$$

$$v = u - \frac{1}{m} \ln \left(1 - \frac{\bar{p}}{\bar{a}}\right),$$

and

$$DF_0(P) = \begin{pmatrix} m(\bar{a} - \bar{p}) & -m(\bar{a} - \bar{p}) \\ -\frac{\bar{b}}{3} \left(1 - \frac{\bar{p}}{\bar{a}}\right)^{1/m} - \frac{2}{3}(\bar{c} + \bar{q}) & \bar{b} \left(1 - \frac{\bar{p}}{\bar{a}}\right)^{1/m} \end{pmatrix},$$

so its degree is equal to 1, provided that  $P \in (\alpha, \beta) \times (\alpha, \beta)$ . Next, let  $F_\lambda(u, v) = (0, 0)$  with  $\lambda \in (0, 1)$ . When  $\eta$  is a critical point of  $u$  we deduce

$$1 - e^{m(u(\eta)-v(\eta))} = \frac{p(\eta)}{a(\eta)},$$

and hence

$$u_{max} \leq v_{max} + \frac{1}{m} \ln \left(1 - \left(\frac{p}{a}\right)_{min}\right),$$

$$u_{min} \geq v_{min} + \frac{1}{m} \ln \left(1 - \left(\frac{p}{a}\right)_{max}\right). \tag{17}$$

We proceed as in Model 1: if  $\xi$  is a global maximum of  $v$ , then (13) holds and hence

$$e^{2/3u(h(\xi))} \leq \left(\frac{b(1 - (\frac{p}{a})_{min})^{1/m} - c - q}{d}\right)_{max}.$$

Thus,

$$u(h(\xi)) \leq \frac{3}{2} \left(\frac{b(1 - (\frac{p}{a})_{min})^{1/m} - c - q}{d}\right)_{max} := k_3,$$

and (13) yields

$$c(\xi) + q(\xi) < b(\xi)e^{k_3}e^{-v_{max}}.$$

This implies

$$v_{max} < k_3 + \ln \left(\frac{b}{c + q}\right)_{max} := \beta$$

$$u_{max} < k_3 + \ln \left(\frac{b}{c + q}\right)_{max} + \frac{1}{m} \ln \left(1 - \left(\frac{p}{a}\right)_{min}\right) < \beta.$$

**Remark 3.1.** It is readily seen that

$$\beta > \frac{3}{2} \ln \frac{\bar{b} \left(1 - \frac{\bar{p}}{\bar{a}}\right)^{1/m} - \bar{c} - \bar{q}}{\bar{d}} - \frac{1}{m} \ln \left(1 - \frac{\bar{p}}{\bar{a}}\right).$$

Thus, if we set, as before,  $P = (u, v) \in \mathbb{R}^2$  as the unique zero of  $F_0$ , then  $u < v < \beta$ .

On the other hand, if  $\xi$  is a global minimum of  $v$ , then again from (13)

$$u(h(\xi)) < v_{\min} + \ln \left( \frac{c+q}{b} \right)_{\max} + \gamma e^{2/3v_{\min}},$$

where  $\gamma$  is defined by (14) and  $M$  is now given by

$$M(\xi) := \ln \frac{c(\xi) + q(\xi) + d(\xi) \left(1 - \left(\frac{p}{a}\right)_{\min}\right)^{2/3m} e^{2/3\beta}}{b(\xi)}.$$

Combining with (17), the last inequality yields

$$\frac{1}{m} \ln \left(1 - \left(\frac{p}{a}\right)_{\max}\right) < \ln \left(\frac{c+q}{b}\right)_{\max} + \gamma e^{2/3v_{\min}},$$

so we conclude

$$v_{\min} > \frac{3}{2} \ln \frac{\ln \left[ \left(1 - \left(\frac{p}{a}\right)_{\max}\right)^{1/m} \left(\frac{b}{c+q}\right)_{\min} \right]}{\gamma}.$$

Thus, it suffices to choose  $\alpha$  smaller than the minimum between two quantities

$$\frac{3}{2} \ln \frac{\ln \left[ \left(1 - \left(\frac{p}{a}\right)_{\max}\right)^{1/m} \left(\frac{b}{c+q}\right)_{\min} \right]}{\gamma}$$

and

$$\frac{3}{2} \ln \frac{\bar{b} \left(1 - \frac{\bar{p}}{\bar{a}}\right)^{1/m} - \bar{c} - \bar{q}}{\bar{d}}. \quad \square$$

**Corollary 3.3.** *The following upper estimates hold for the solutions of Model 3*

$$u_{\max} - \frac{1}{m} \ln \left(1 - \left(\frac{p}{a}\right)_{\min}\right) \leq v_{\max} < k_3 + \ln \left(\frac{b}{c+q}\right)_{\max}.$$

Moreover, if the assumption of Theorem 3.3 is satisfied, then the following lower estimates also hold

$$u_{\min} - \frac{1}{m} \ln \left(1 - \left(\frac{p}{a}\right)_{\min}\right) \geq v_{\min} > \frac{3}{2} \ln \frac{\ln \left[ \left(1 - \left(\frac{p}{a}\right)_{\max}\right)^{1/m} \left(\frac{b}{c+q}\right)_{\min} \right]}{\gamma}.$$

### 3.4. Existence of periodic solutions: necessary conditions

In summation, the proofs of the preceding theorems reveal that the sufficient conditions are ‘almost’ necessary, in the following sense.

**Theorem 3.4.** *Assume that problem (2) admits a positive  $T$ -periodic solution. Then  $b(t) > (c(t) + q(t))e^{(p/a)_{\min}}$  for some  $t$ .*

**Proof.** As in the proof of Theorem 3.1, if  $(u, v)$  is a  $T$ -periodic solution of (5) we deduce that

$$u_{\max} \leq v_{\max} - \left(\frac{p}{a}\right)_{\min}.$$

Moreover, if  $\xi$  is an absolute maximum of  $v$  then (13) holds and hence

$$0 < d(\xi)e^{2/3u(h(\xi))} = b(\xi)e^{u(h(\xi))-v_{\max}} - c(\xi) - q(\xi) \leq b(\xi)e^{-\left(\frac{p}{a}\right)_{\min}} - c(\xi) - q(\xi). \quad \square$$

**Theorem 3.5.** *Assume that problem (3) admits a positive  $T$ -periodic solution. Then  $\bar{b} > \bar{c} + \bar{q}$ .*

**Proof.** Let  $(u, v)$  be a  $T$ -periodic solution of (6). Integrating the second equation of the system it is readily seen that

$$\bar{b} = \bar{c} + \bar{q} + \frac{1}{T} \int_0^T d(t)e^{2/3u(h(t))} dt > \bar{c} + \bar{q}. \quad \square$$

**Theorem 3.6.** *Assume that problem (4) admits a positive  $T$ -periodic solution. Then  $\left(\frac{c(t)+q(t)}{b(t)}\right)^m + \left(\frac{p}{a}\right)_{\min} < 1$  for some  $t$ .*

**Proof.** Let  $(u, v)$  be a  $T$ -periodic solution of (7). Then the inequalities (17) are satisfied. Moreover, if  $\xi$  is a maximum of  $v$  then (13) holds and

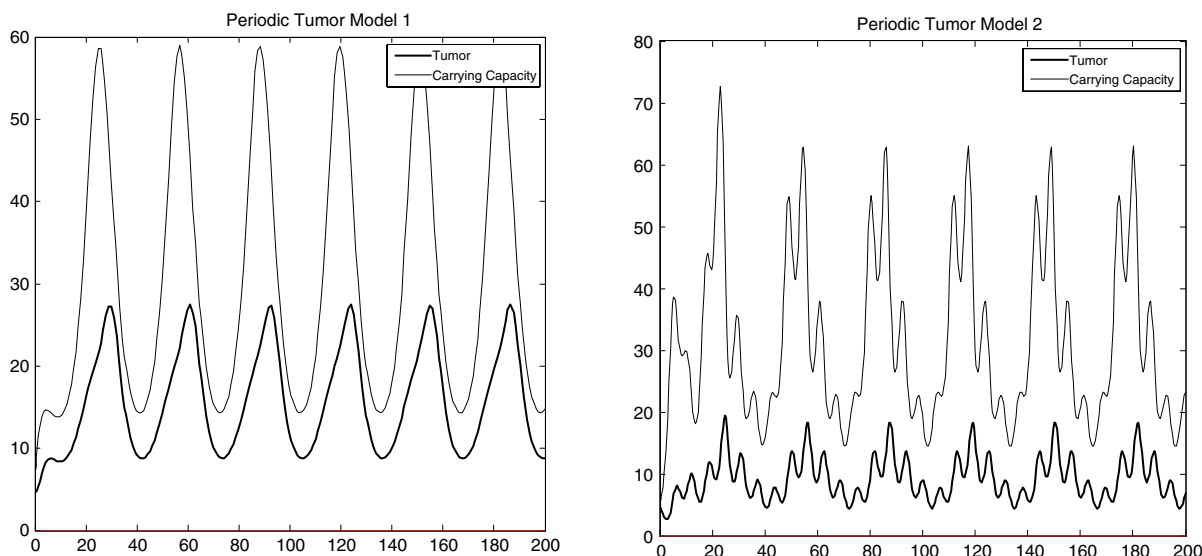
$$0 < d(\xi)e^{2/3u(h(\xi))} = b(\xi)e^{u(h(\xi))-v_{max}} - c(\xi) - q(\xi) \leq b(\xi) \left(1 - \left(\frac{p}{a}\right)_{min}\right)^{1/m} - c(\xi) - q(\xi).$$

This implies that

$$\frac{c(\xi) + q(\xi)}{b(\xi)} < \left(1 - \left(\frac{p}{a}\right)_{min}\right)^{1/m}$$

and so completes the proof.  $\square$

The following graphs illustrate that if all conditions of Theorems 3.1 and 3.3 are satisfied, then positive periodic solutions exist (Fig. 1).



**Fig. 1.** Existence of positive periodic solutions with the parameters given by (a) data set for model:  $a = .5 \sin(.2t) + 0.6, p = 0.25 \sin(.2t) + 0.3, b = 2.5, c = 0.0, q = 0.1 \sin(0.2t) + 0.2, d = 0.1 \sin(.2t) + 0.2, \tau = 0.1$ ; (b) data set for model 2:  $a = .25, p = 0.25 \sin(t) + 0.34, b = 1.5, c = 0.25 \sin(0.2t) + 0.3, q = 0.1, d = 0.25, \tau = 0.1$ .

#### 4. Concluding remarks

In Section 3.2 a Liénard-type second-order differential equation with delays was used as an alternative tool for the proof of the existence of the periodic solutions of Model 2. The interesting fact about this approach is that, under slightly different conditions, we obtained *a priori* estimates directly from the second order equation. Definitely, if the assumptions of Theorems 3.1 and 3.3 hold, then this approach can be used for Model 1 and Model 3. We think that an interesting question would be: is it possible to get lower estimates for Model 1 and Model 3 via a Liénard-type equation, when the assumptions of Theorems 3.1 and 3.3 are dropped? Another open problem would be further studies of the uniqueness or multiplicity of the solutions.

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